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Adverse Reactions to Chloroquine and Amodiaquine as Used for Malaria Prophylaxis: A Review of the Literature

SUMMARY

This paper reviews the published material on adverse reactions to chloroquine (CQ) and amodiaquine (ADQ) as used for anti-malarial chemophrophylaxis. Dermatologic reactions, including pruritus and photosensitivity, appear to be rather common. Ophthalmologic reactions include difficulty in visual accommodation, corneal deposits, and retinopathy, the last a serious condition that is reversible in its early stage by drug withdrawal, and that generally will not occur with less than four years of weekly CQ use. Neuromyopathy is a rare and serious reaction that may develop idiosyncratically after a small cumulative dose; it, too, is reversible by drug withdrawal. Seizures, syndromes of involuntary movements, psychosis, and ototoxicity have been reported occasionally. Fatal toxic overdoses may occur, especially following accidental ingestion by children. ADQ should not be used for anti-malarial prophylaxis because of associated agranulocytosis. Rabies vaccine given intradermally is less effective for pre-exposure prophylaxis while the patient is taking CQ. Care should be taken when prescribing prophylactic CQ to patients with heart block. In spite of its adverse effects, however, CQ is generally an extremely safe drug. CQ prophylaxis is recommended for pregnant women in CQ-sensitive malarial areas. (*Can Fam Physician* 1987; 33:2644–2649.)

RÉSUMÉ

Cet article révise la littérature concernant les effets secondaires de la chloroquine (CQ) et de l'amodiaquine (ADQ) utilisées dans la chimioprophylaxie antimalarique. Certaines réactions dermatologiques telles le prurit et la photosensibilité semblent plutôt courantes. Les réactions ophtalmologiques incluent la difficulté d'accommodation visuelle, les dépôts cornéens et la rétinopathie. Cette dernière réaction constitue une affection sérieuse mais réversible si l'on cesse précocément le médicament et qui ne se manifeste généralement qu'après quatre ans d'usage hebdomadaire de chloroquine. La neuromyopathie est une réaction rare et sérieuse qui peut se développer de façon idiosyncrasique suite à l'ingestion d'une faible dose cumulative; le retrait médicamenteux en permet aussi la réversibilité. Convulsions, syndromes de mouvements involontaires, psychose et ototoxicité ont été rapportés occasionnellement. Les intoxications fatales peuvent s'avérer un problème, surtout suite à une ingestion accidentelle par des enfants. L'ADQ ne devrait pas être administrée comme prophylaxie antimalarique à cause du risque d'agranulocytose. Chez le patient traité à la CQ, le vaccin contre la rage par voie intradermique est moins efficace comme prophylaxie en pré-exposition, et ses effets sur les réponses immunitaires aux autres vaccins nécessitent une étude plus poussée. L'usage prophylactique de la CQ est contre-indiqué chez les patients qui présentent un bloc cardiaque. Chez les femmes enceintes, toutefois, l'usage prophylactique de la CQ est recommandé contre le paludisme, dans les régions où la malaria est sensible à la chloroquine.

Key words: malaria, chloroquine, amodiaquine, chemoprophylaxis, treatment

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CHLOROQUINE (CQ) is the drug of first choice for the chemoprophylaxis of CQ-sensitive species of malaria, and prophylactic CQ is recommended for use in all malarial areas of the world, including those areas where CQ-resistant strains of *Plasmodium falciparum* exist.[1–3] CQ is one of a large series of 4-aminoquinolines that were investigated for use as antimalarials and that have subsequently been used in auto-immune disorders as well. The only 4-aminoquinoline available in Canada for malaria che-

moprophylaxis is CQ phosphate (Aralen®), at a recommended adult dose of 500mg of the salt (=300mg of the base) per week. CQ sulfate (Nivaquine®) is available and is often recommended abroad. Amodiaquine (ADQ) (Flavoquine®, Camoquin®) is no longer recommended for malaria chemoprophylaxis, but remains available abroad. Hydroxychloroquine (HCQ) (Plaquenil®) is available in Canada but is used generally for rheumatoid arthritis and other immunologic disorders, and is not usually recommended for either the chemoprophylaxis or the treatment of malaria.

As used for the chemoprophylaxis and treatment of malaria, CQ is a very safe drug, and adverse or serious side-effects are only rarely reported. Such reactions may occur, however, and with the increase in foreign travel, physicians must be aware of them. Herein follows a review of the major published adverse reactions to the 4-aminoquinolines as used for malaria chemoprophylaxis. They are described in terms of dermatologic reactions, ophthalmologic effects, neuromyopathy, neuropsychiatric reactions, acute toxic overdose, hematologic reactions, effect on concurrent vaccine administration, miscellaneous reactions, and teratogenic effects. Unless otherwise stated, all dosages mentioned in this review are in terms of the salt, not the base. The frequency rate of any of these side-effects is unknown, as there exist no denominator data on the number of people who have used 4-aminoquinolines for malaria chemoprophylaxis. It can be assumed, however, that serious adverse reactions that have been reported only rarely do, in fact, occur only rarely.

Dermatologic Reactions

Previously reported dermatologic reactions to 4-aminoquinolines have included pruritus, photosensitivity, lichen-planus-like eruptions, and pigmentation changes. Although urticaria has been noted anecdotally in the literature,[4] a review of the literature disclosed no actual case reports.

Photosensitivity reactions have rarely been reported in individuals.[5] In a chloroquinized salt campaign in Guyana, however, where individuals were ingesting varying amounts of CQ daily for malaria prophylaxis, a photoallergic dermatitis developed in about 1% of the population. The lesions ranged in severity from nummular erythematous eruptions to severe exfoliative dermatitis; they were more common among lighter-skinned people.[6] The racial distribution of CQ-induced pruritus is quite the reverse. It has been reported only once in a Caucasian,[7] but has been commonly found among Black Africans.[8] In one survey, 28% of Nigerians who had taken 4-aminoquinolines reported pruritus.[9] However, pruritus is not considered a contraindication to the use of aminoquinolines.

Among a group of 30 volunteers taking CQ for one year in a weekly dose of 833mg, two persons developed cutaneous eruptions that began eight and 12 months after they commenced taking CQ. These were scaly maculopapular eruptions on the trunk and upper limbs of a lichen-planus-like gross and histologic appearance.[10, 11] Another case of nummular erythematous scaly psoriatic lesions, not confined to sun-exposed areas, has been reported.[12] Finally, rare cases of CQ-induced pigmentation disorders have occurred. These have included bleaching of hair,[13] as well as generalized hyperpigmentation;[14, 15] in the latter cases, biopsies of hyperpigmented areas disclosed melanin-chloroquine complexes.[14] Similar skin-hyperpigmentation lesions have been induced by phenothiazines. Any of these dermatologic reactions should dictate substitution of an unrelated anti-malarial such as pyrimethamine or proguanil.

Ophthalmologic Reactions

On beginning CQ or ADQ, many patients report a difficulty in changing focus quickly between near and far objects.[4, 10, 16] This difficulty in accommodation is thought to result from a stabilization of the action potential of the membranes in the ciliary muscles by competing with calcium ions for binding sites.[4] Generally, this initial symptom resolves after a few weeks, and it causes no permanent visual sequelae.

Corneal deposits may occur. Fifty per cent of patients with these deposits are asymptomatic, while the others report the presence of halos around light sources, flashing lights, and photophobia.[16] Pathologic examination of these corneal deposits in one case of ADQ toxicity showed intracytoplasmic inclusion bodies in the corneal epithelium, similar to those seen in a number of drug-induced phospholipidoses.[17] The corneal deposits resolve completely on discontinuance of the drug.[16, 17]

Retinopathy is the most serious ophthalmologic effect and the most common of the serious adverse effects of CQ and ADQ. The symptoms of this retinopathy include difficulty reading (as though words or letters are missing), blurred distance vision, blacked-out areas in the visual fields, light flashes, and photophobia. The fundoscopic findings consist initially of macular hyperpigmentation surrounded by a clear zone of depigmentation. Later, there is constriction of retinal arterioles with pallor of the optic disc and a corresponding loss of visual fields. Visual testing may show central scotomata and later defects in peripheral visual fields, impaired color vision, and abnormal electrooculograms and electroretinograms.[16, 17]

The pathophysiology of CQ retinopathy has not been fully elucidated. It is known that CQ concentrates in melanin-containing tissues, where its concentration is higher than in any other tissues and is approximately 1,000 times the plasma concentration.[18, 19] Furthermore, while the tissue half-life of CQ on discontinuance of the drug is about seven days, the excretion of small amounts of CQ may be detected in the urine for as long as five years after the last known administration.[20] The high concentration of CQ in the melanin-containing retinal pigmented epithelium seems to be responsible for the retinopathy. It has been postulated that this occurs because CQ interferes with lysosomal function, interfering with the scavenging function of the retinal pigmented epithelium to phagocytose photoreceptor discs that are shed diurnally from rod and cone cells.[4, 16, 17, 19] Similar findings have been used to explain the corneal deposits and the pigmentary retinopathy caused by phenothiazines.[21]

CQ retinopathy has been linked to high daily dosage over many years (as used in the treatment of rheumatoid arthritis and systemic lupus erythematosus). Few cases have been reported in patients on a daily dose of less than 250mg of CQ, or 4mg/kg body weight, and most cases have occurred in patients on a daily dose exceeding 500mg. Taken as a daily dose, an accumulation of 100g salt of CQ (250mg per day for one year) may cause reti-

nopathy, but the risk significantly increases only when the total accumulated dosage surpasses 300g.[16, 22, 23] Although this is generally true, there may also be occasional toxic phenomena at an idiosyncratically low total dose. (See "Neuromyopathy" below.) In a similar vein, a case of pigmentary retinopathy resulting from a low daily dose of the phenothiazine thioridazine was recently reported.[24]

Retinal changes occur prior to the onset of abnormalities in visual testing or visual symptoms, and the retinopathy at this time is completely reversible on discontinuance of the drug. Later the retinopathy becomes irreversible and even progressive after discontinuance of the drug. If ophthalmoscopic examination is done on patients taking a daily dose of CQ after a cumulative dose of 100g salt, and at every 100g thereafter, the risk of irreversible CQ retinopathy approaches zero.[16]

It is not clear what the implications of the above observations are for patients taking CQ for malaria prophylaxis. There have been few reported cases of retinopathy among patients taking weekly (as compared to daily) CQ, and it has been suggested that it is the total daily dosage rate, and not the cumulative dose, that determines the development of retinopathy.[22] Nonetheless, it seems prudent to advise that patients taking weekly CQ be assessed by an ophthalmologist after four years of taking CQ, 500mg per week (yielding a cumulative dose of 100g salt).

A final point to be made is that the CQ congener hydroxychloroquine (HCQ) is two to three times less toxic in animals than is CQ, and at identical plasma concentrations, HCQ has only 40% of the tissue concentrations of CQ.[18] HCQ is generally safer than CQ, and specifically safer as regards retinopathy.[16, 18, 19, 22, 23, 25] Although HCQ was developed as an alternative to CQ as an anti-malarial,[26] and although it is less toxic than CQ, it has nonetheless not been widely used or recommended as an anti-malarial. Therefore its use in this context cannot be advocated, but clinical trials of HCQ for malaria prophylaxis could prove worthwhile.

Neuromyopathy

Twenty cases have previously been reported of neuromyopathy that developed in patients who were taking CQ or ADQ.[27–36] The symptoms were weakness of the proximal muscles, initially of the legs and then of the trunk, neck, and shoulders. Eighteen patients had been taking CQ or ADQ on a daily basis for non-malarial reasons including rheumatoid arthritis and systemic lupus erythematosus, but in all cases the neuromyopathy was almost definitely secondary to the drug as compared to the underlying disease. Two patients had been taking weekly CQ or ADQ for malaria prophylaxis, at 150%–300% of the recommended dosage.[33, 34]

Discontinuance of the drug led to improvement in symptoms within two to four weeks, with complete recovery from symptoms, abnormal physical signs, and abnormal electromyelograms (EMG's) in one to 15 months. The cumulative dose had been 45–1,000g taken over a period of several weeks to four years, but beginning after a minimum of six months in 17 of the 20 patients. In a recent case report of ADQ neuromyopathy, a patient had been taking weekly ADQ at 50% greater than the recommended dose for malaria chemoprophylaxis for 10 months, for a total cumulative dose of 31g, prior to the onset of her symptoms.[34] Physical examination of all of these patients showed muscle weakness and diminished or absent deep tendon reflexes of the involved muscles. The only serum abnormality was frequently a slight elevation of the serum levels of glutamic oxaloacetic transaminase (SGOT) and creatinine phosphokinase (CPK). EMG and nerve conduction studies showed abnormal muscle fibrillations and irritability, diminished motor-unit amplitude and duration, and loss in the number of recruited motor units. Motor-nerve conduction was either normal or diminished, and afferent sensory nerve conduction was always intact. The 20 cases were generally considered to represent a primary myopathy, although in some of the cases there also existed the possibility of an independent lower motor neuron neuropathy.

Fifteen of the 20 patients underwent muscle biopsy; two of these showed normal results, and five showed degenerative changes. The remaining eight biopsies showed a vacuolar myopathy;[28–32] the vacuoles contained glycogen in the four cases where specific histochemical tests were done.[29, 32] Along a similar line, experimental studies of chronic toxicity of oral CQ given to rats disclosed some cases of focal necrosis and fibrosis of striated muscle.[36, 37] These vacuoles may represent a similar pathologic process to the ocular toxicity, especially to the intracytoplasmic inclusions in corneal epithelium.[17] Furthermore, among the 11 of the above 20 patients who were evaluated by an ophthalmologist, nine exhibited the typical corneal or retinal changes associated with CQ and ADQ.

Neuromyopathy seems to be a rare but definite adverse reaction of CQ and ADQ. While both the neuromyopathy and the keratopathy/retinopathy usually develop after prolonged daily doses, it seems that both may idiosyncratically develop after a small cumulative dose.

Neuropsychiatric Reactions

Four cases were reported of *grand mal* seizures on CQ therapy for *Entamoeba histolytica*, only one of which had evidence for extra-intestinal amoebiasis. Three of the four had no previous or subsequent history of seizures or of abnormal electroencephalograms (EEGs), but had taken a cumulative dose of 2g–4g over two to six days.[38] Where studied, CQ has had varying effects on the EEG.[39] Ten cases have been reported of CQ-induced psychosis on cumulative doses of 2g–6g over two to four days. The symptoms were agitation, hallucinations, disorientation, and change in sensorium.[39–41] It has been suggested that some cases of fatal CQ overdoses were not voluntary overdoses *per se*, but rather occurred "involuntarily" as a result of drug automatism.[39]

Twenty cases of acute syndromes of involuntary movements induced by CQ or ADQ treatment of malaria have been reported.[42–44] These consisted of acute dystonic movements of the tongue, face, and neck, including buccofacial movements with salivation, torticollis, and oculogyric crisis. These were identical to the dyskinesias sometimes induced by phenothiazines, and the appropriate treatment for both are such anti-cholinergic drugs as benztropine. Both 4-aminoquinolines and phenothiazines, in their avid attachment to melanin, may also block dopaminergic receptors in the brain, since dopa is a precursor of melanin.[45]

Acute Toxic Overdose

In a review of published cases up to 1982, a total of 134 CQ overdoses with toxic effects were found, of which over 75% proved fatal.[39] Many of

these followed accidental ingestion by children, and so parents must ensure that these drugs are kept in child-proof containers. Lethal doses may occur with as little as 2g–4g in adults, and is almost invariable with 8g–10g. There is a two- to three-fold discrepancy between this and toxicity studies in rats, where the LD_{50} is 330mg/kg.[46] Acute toxic overdoses cause weakness, dysphagia, dyspnea, hypotension, tremours, convulsions, coma, cardiac arrythmias, cardiogenic shock, and respiratory arrest.[47, 48] Suggested treatment for toxic overdoses has been acidifying the urine with ammonium chloride and administering dimercaprol to increase the urinary excretion of CQ.[49] A recent experimental study on rats suggested that administration of diazepam may be effective.[46]

Hematologic Reactions

Twenty-five cases of agranulocytosis have recently occurred in people taking ADQ (23 in the last two years), of whom 21 were taking the appropriate dosage for malaria chemoprophylaxis.[50, 51] Seven of the cases were fatal. Fourteen of the patients were known to have been using another anti-malarial prophylactic drug concurrently (either pyrimethamine-sulfadoxine or proguanil). In the previous 30 years, there had been only three cases of agranulocytosis in people taking ADQ for malaria chemoprophylaxis. Whether the recent dramatic increase in cases of ADQ-agranulocytosis was caused by increased use of ADQ alone for chemoprophylaxis, increased use of other drugs along with ADQ for chemoprophylaxis, or some other factors remains unknown. However, these cases prompted the Centers for Disease Control to cease recommending the use of ADQ for anti-malarial chemoprophylaxis;[51] nonetheless, the drug remains available and may often be used for this purpose in malaria-endemic regions.

CQ may cause an exacerbation of symptoms in patients with porphyria hepatica of the mixed type or porphyria cutanea tarda.[52] In northern India, three male children with G-6-PD deficiency developed acute severe intravascular hemolysis on receiving the standard CQ dosage for the treatment of malaria.[53] As contrasted with primaquine, which has often been implicated as the cause of hemolysis in G-6-PD-deficient patients, there have been no other reports of CQ-induced hemolysis. Some suggest that care should perhaps be taken among G-6-PD-deficient persons from India and the Mediterranean, who seem to be more susceptible to drug-induced hemolysis than are G-6-PD-deficient Blacks.[53] However, G-6-PD deficiency does not constitute a contra-indication to CQ.

Effects on Concurrent Vaccine Administration

An American woman in Kenya died of rabies three months after being bitten by her pet dog. Although she received no post-exposure rabies prophylaxis, she had received the recommended intra-dermal dosage of human diploid-cell rabies vaccine (HDCV) for pre-exposure prophylaxis six months before the dog bite, while taking CQ anti-malarial prophylaxis.[54] This event led to a prospective trial of 51 veterinary-student volunteers, who received the standard vaccination regime for rabies pre-exposure prophylaxis by the intra-dermal route of HDCV; 26 also took concurrent CQ, 500mg per week, while 25 did not.[55] The post-vaccination mean rabies-neutralizing antibody titre for the CQ group was significantly lower than that for the control group, and there was an inverse relationship between blood levels of CQ and antibody titres to rabies. It was speculated that CQ interference with lysosomal function within macrophages had led to diminished T-cell-dependent antibody production to HDCV. Subsequently, it was recommended that HDCV pre-exposure prophylaxis could be given either by way of the intra-dermal or by way of the intra-muscular route if the person were not concurrently taking CQ; it should be administered only by way of the intra-muscular route and dosage if the person is taking CQ prophylaxis.[56]

No significant reduction in vaccine-induced antibody responses between persons taking CQ as compared to those not taking CQ were observed following a tetanus-measles-meningococcal vaccine in Nigeria[57] or following the injection of pneumococcal polysaccharide vaccine in patients with systemic lupus erythematosus.[58] However, it has been pointed out that the effects of CQ on vaccine response are difficult to evaluate in the presence of other factors affecting the immune response (such as endemic malaria or lupus), and that further controlled trials are indicated.[59]

Miscellaneous Reactions

Minor electrocardiographic changes (diminution of the height of T-waves) have been noted with chronic administration of CQ, but these resolved following discontinuance of the drug.[10] However, syncope has been described in three patients who had heart block—complete in two cases and fatal in one—attributable to CQ, 250mg weekly for two to three years. All three had CQ retinopathy.[60, 61] It has been suggested, too, that the CQ neuromyopathy may also involve cardiac muscle, causing a vacuolar cardiomyopathy.[32, 62] It is recommended that patients with a known history of heart disease who will be prescribed prophylactic CQ be given an electrocardiogram, and that heart block be considered a relative contra-indication to the prophylactic use of CQ.

Tinnitus, vertigo, and a few cases of nerve deafness have occurred on prolonged daily doses of 4-aminoquinolines.[63] A total of 16 cases of acute CQ-induced sensorineural deafness have also been reported, and this has been attributed to the affinity of CQ for melanin-containing cells in the stria vascularis of the cochlea and in the ampullae of the semi-circular canals.[64, 65] Ototoxicity in the fetus will be discussed below.

Teratogenic Effects

Only two cases have been documented of probable CQ teratogenicity. The first case involved a woman with discoid lupus erythematosus who was taking CQ, 250mg–500mg daily, for various time periods during four of her seven pregnancies.[66] The children born of her three drug-free pregnancies were perfectly normal. Of the other four pregnancies, one resulted in a spontaneous abortion, and three children were born with congenital abnormalities. Two had severe cochleovestibular and dorsal column spinal cord abnormalities, while a third had unilateral limb abnormalities. All of these children, as well as the mother, had retinal pigmentary changes typical of CQ retinopathy. Although eighth-nerve injury and retinal pigment abnormalities may occur together as a hereditary trait, it was considered that CQ was a very likely cause of these congenital abnormalities.[66, 67]

The second case, recently reported, involved a woman who contracted *Plasmodium falciparum* malaria during the first trimester of her first pregnancy while taking CQ, 500mg weekly. Her child was born with unilateral limb abnormalities, and a subsequent pregnancy resulted in a perfectly normal child.[68] The role of CQ in the congenital anomalies in this case is far from being certain.

It is generally agreed that in CQ-sensitive areas, the risk of malaria and its effects on both the pregnant "non-immune" woman and the fetus far outweigh the possible teratogenicity of CQ. Therefore, pregnant women from non-endemic areas who go to reside in a CQ-sensitive malaria-endemic area are advised to take CQ prophylaxis.[69–71]

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Answer to Dermacase (page 2468)

4. Perioral dermatitis

This condition was first described by Mihan and Ayres in 1964.[1] It is characterized by red papules and, less often, by pustules on the face about the mouth, naso-labial folds, and sometimes around the eyes. The surface of the affected skin may show a fine scaling. The condition is usually asymptomatic. The lesions can come on rather suddenly, and will wax and wane over several weeks. If untreated, the condition may last for several years.[2]

Perioral dermatitis appears to be a condition exclusive virtually to females between the ages of 16 and 50 years, though it has been seen on rare occasions in young males. The cause of this condition is unknown. Several causal factors have been promoted, such as ultra-violet light, candida and bacterial infections, contact agents, topical steroids, and hormonal factors.[3] The predominance of the condition in women, the pre-menstrual flare-up, and the extensive involvement during pregnancy tend to suggest some sort of hormonal association.

Though biopsy for histologic examination is not often taken, the changes are generally non specific, with a mild sub-acute inflammation and accumulation of the inflammatory cells about the follicles and vessels.

In the typical case, the diagnosis gives little trouble. The condition may, however, be confused with rosacea, acne, or seborrheic dermatitis. Rosacea is more centrally located, and lesions are prominent on the nose. In addition, the inflammatory papules are larger and often pustular or cystic. Erythema and telangiectasia are also prominent in rosacea. The use of strong topical corticosteroids will often confuse the picture, since this treatment may create telangiectasia. Acne generally shows comedones, large inflammatory papules and pustules, and lesions on the periphery of the face. Very often women with perioral dermatitis are greatly distressed, since they have had little or no acne problems.

Since its recognition in 1964, a variety of topical and systemic medications have been tried to relieve perioral dermatitis. The treatment that gives the greatest success is oral tetracycline.[4] The medication is given for six weeks or more, using an initial dose of 750mg/day and reducing to 250mg/daily after three weeks. Patients who do not respond to tetracycline may be treated with minocycline (50mg b.i.d.). In most cases the response to treatment is excellent, and the incidence of recurrence is very low. ◉

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